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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,747	KOBAYASHI ET AL.	
	Examiner	Art Unit	
	NARAYAN K. BHAT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-19 and 21-34* is/are pending in the application.

4a) Of the above claim(s) *8-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 19 and 21-34* is/are rejected.

7)☒ Claim(s) *26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 27, 2009 has been entered.

Claim Status

2. This action is in response to papers filed on August 27, 2009. Claims 1-19 and 21-34 are pending in this application.

3. Claims 1, 2, 4, 19, 21, 25, 27 and 28 are amended. New claims 29-34 are added. Claim amendments have been reviewed and entered.

4. Applicant's arguments filed August 27, 2009 have been thoroughly reviewed and addressed following the rejections.

5. Claims 8-16 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and Applicant's timely traversed election requirement made final on June 12, 2007.

6. Claims 1-7, 17, 19 and 21-34 are under examination.

Claim Objections -Duplicate claim warning

7. Claim 26 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 19. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim (See MPEP § 706.03(k)). In the instant case claim 26 which is dependent from claim 19, fails to further limit the parent claim.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 19 and its dependent claims 21-27 and 33-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 19 recites the limitation "said plastic substrate" in line 3. There is insufficient antecedent basis for "plastic" limitation in the claim.

11. Claims 21-27 and 33-34 are indefinite because they are dependent from claim 19.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 1-7, 17, 28-30 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Henderson et al (USPGPUB 2003/0186311 filed Apr. 30, 2003, effective filing date May 29, 1999).

Regarding claim 1, Henderson et al teaches a molecular detection method comprising visualizing and identifying an individual chain molecule 10 (i.e., single molecule) immobilized on a substrate surface 12 and as immobilized being uprightly disposed relative to substrate surface 12 by probing with a scanning probe microscope (i.e., AFM) in solution (Fig. 1A and paragraphs 0040-0041, Example 4 and paragraphs 0089-0092). Henderson et al also teaches substrate comprise plastic substrate surface (paragraph 0029). Henderson et al also teaches observing a profile of the substrate surface having individual antibody chain molecules 10 immobilized thereon (Figs. 1 and 2, paragraph 0047).

Regarding claim 2, Henderson et al teaches that the protein chain molecule 30 immobilized on the plastic substrate surface 32 is an uprightly disposed single strand molecule (Fig. 1 B and paragraph 0042).

Regarding claim 3, Henderson et al teaches that the uprightly disposed single strand molecule is a nucleic acid, a peptide and a synthetic amino acid polymer (Example 2 and paragraphs 0026 and 0078-0081).

Regarding claim 4, Henderson et al teaches that the chain molecule immobilized on the plastic substrate surface 12 is a multiple strand molecule 10/14 comprising an uprightly disposed single strand molecule 10 and at least one chain molecule 14 that can bind to the single strand molecule (Fig. 1 and paragraph 0041)

Regarding claim 5, Henderson et al teaches that the multiple strand molecule is a complex of a peptide and antibody (Fig. 1 and Example 2).

Regarding claim 6, Henderson et al teaches that the detecting a molecule comprises counting the number of detected chain molecules per unit area (Example 5 and paragraphs 0030 and 0098, Table 1).

Regarding claim 7, Henderson et al teaches that the counting the number of detected chain molecules per unit area, thus giving molecular localization information (Fig. 7, Example 5 and paragraphs 0030 and 0099).

Regarding claim 17, Henderson et al teaches a production process for a substrate with a chain molecule immobilized thereon, the production process as recited in claim 1 (Fig. 1 and paragraph 0041).

Regarding claim 28, Henderson et al teaches that the individual chain molecule 10, as immobilized, is uprightly disposed relative to the substrate surface 12 so as to extend substantially perpendicularly from substrate surface 12 (Fig. 1 and paragraph 0041) and further teaches substrate comprises plastic surface (paragraph 0029).

Regarding claim 29, Henderson et al teaches that the profile is observed using atomic force acting between the substrate surface having the individual chain molecules immobilized thereon and a probe of the scanning probe microscope (Fig. 1 and

paragraphs 0058-0062). Henderson et al also teaches AFM is used to profile binding force as a result of molecular interaction between probe on the substrate surface and the binding partners and rupture force to break the said molecular interactions (paragraphs 0052-0053), which is reasonably interpreted as atomic force in view of lack of limiting definition for "atomic force" in the instant specification.

Regarding claim 30, Henderson et al teaches that the profile is observed by measuring an amount of rupture force, i.e., flexing of probe caused by disruption of molecular interaction between the binding partner and probe on the substrate force (paragraphs 0051-0054). The "rupture force" of Henderson et al is reasonably interpreted as atomic force in view of lack of limiting definition for "atomic force" in the instant specification.

Regarding claim 32, Henderson et al teaches that the substrate having a chain molecule immobilized there on is a protein array (Example 2, paragraphs 0075-0082) and is protein chip as defined in the instant specification (USPGPUB paragraph 0063).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-5, 17, 19, 21, 22 and 25-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (Nano Letters, 2002, 2, 863-867) in view of Obremski et al (USPGPUB NO. 2002/0001853 published Jan. 3, 2002) and further in view of Seong et al (Anal. Chem. 2000, 72, 1288-1293).

Regarding claim 1, Liu et al teaches a molecular detection method comprising visualizing and identifying chain molecule (Figs. 4A and 4G, pg. 865, column 2, paragraph 3) immobilized on a substrate and immobilized being uprightly disposed relative to said substrate (Fig. 1, pg. 865, column 1, paragraph 1, pg. 866, column 2, paragraph 1, lines 3-6) by probing with scanning probe microscope in solution so as to observe profile of the chain molecules immobilized on the substrate surface (Abstract, Figs. 3A and 4A, pg. 865, column 2, paragraph 2). Liu et al do not teach about plastic substrate and visualizing and identifying an individual chain molecule.

Regarding claim 2, Liu et al teaches that chain molecule (i.e., single stranded DNA) is immobilized on the gold surface (Fig. 2C, pg. 864, column 1, and last paragraph) and is an uprightly disposed single stranded DNA molecule (i.e., stand up configuration, pg.865, column 1, paragraph 1).

Regarding claim 3, Liu et al teaches that the uprightly single strand molecule is a nucleic acid (Fig. 1, pg. 865, column 1, and paragraph 1).

Regarding claim 4, Liu et al teaches that the chain molecule is in stand up position (Fig. 1, pg. 865, column 1, paragraph 1) and the binding of DNase I molecule to the uprightly disposed chain molecule comprises multi-strand molecule.

Regarding claim 5, Liu et al teaches that the multiple strand molecules are a complex of single strand DNA and protein DNaseI (pg. 865, column 2, paragraphs 2 and 3, pg. 866, column 1, paragraph 1).

Regarding claim 17, Liu et al teaches a production process for immobilizing the single stranded DNA, i.e., chain molecule on a substrate (Fig. 2, substrate – labeled as Au (III), pg. 864, column 1, paragraph 4) and further teaches that the immobilized single strand DNA is in uprightly disposed position (Fig. 1, pg. 865, column 1, paragraph 1).

Regarding claim 19, Liu et al teaches a molecular detection method comprising visualizing and identifying chain molecule (Figs. 4A and 4G, pg. 865, column 2, paragraph 3) immobilized on a substrate and as immobilized being uprightly disposed relative to said substrate so as to observe a profile of the substrate surface having chain molecule immobilized there on (Figs. 1 and 4C, pg. 865, column 1, paragraph 1) by probing with scanning probe microscope in solution (Abstract, Figs. 3A and 4A, pg. 865, column 2, paragraph 2), wherein the molecule immobilized on the substrate is a nucleic acid (Fig. 2, pg. 864, column 1, paragraph 3). Liu et al do not teach about plastic substrate and visualizing and identifying an individual chain molecule.

Regarding claim 21, Liu et al teaches that the chain molecule is in stand up position (Fig. 1, pg. 865, column 1, paragraph 1) and the binding of DNase I molecule to the uprightly disposed chain molecule comprises multi-strand molecule.

Regarding claim 22, Liu et al teaches that the multiple strand molecules are a complex of single strand DNA and protein DNaseI (pg. 865, column 2, paragraphs 2 and 3, pg. 866, column 1, paragraph 1).

Regarding claim 25, Liu et al teaches a production process for immobilizing the single stranded DNA, i.e., chain molecule on a substrate (Fig. 2, substrate – labeled as Au (III), pg. 864, column 1, paragraph 4) and further teaches that the immobilized single strand DNA is in uprightly disposed position (Fig. 1, pg. 865, column 1, paragraph 1).

Regarding claim 26, Liu et al teaches the substrate is gold surface (Fig. 2, pg. 864, column 1, last paragraph), but do not teach about plastic surface.

Regarding claims 27 and 28, Liu et al teaches that the molecule, as immobilized, is uprightly disposed relative to the substrate so as to extend substantially perpendicularly from said substrate surface (Figs. 1 and 3A, pg. 865, column 1, paragraph 1, lines 2-4).

Regarding claim 29 and 33, Liu et al teaches that the profile is observed using frictional force acting between the substrate surface having the individual chain molecules immobilized thereon and a probe of the scanning probe microscope (Compare the profile Fig. 4C versus 4H and pg. 866, column 1, paragraph 1). Liu et al also teaches the interaction between the methyl group and the AFM tip corresponds to a frictional force (pg. 866, column 1, paragraph 1, lines 23-28), which is reasonably

interpreted as atomic force in view of lack of limiting definition for "atomic force" in the instant specification.

Regarding claims 30 and 34, Liu et al teaches that the profile is observed by measuring an amount of single stranded DNA left after the DNase I digestion caused by interaction between said DNA and DNAse I (paragraphs 0051-0054). The force required to digest single strand DNA by DNase I of Liu et al is reasonably interpreted as atomic force in view of lack of limiting definition for "atomic force" in the instant specification.

Regarding claim 31, Liu et al teaches that the substrate having a chain molecule immobilized there on is a DNA chip (Fig. 2C)

Regarding claim 32, Liu et al teaches selective immobilization of proteins on the substrate surface (pg. 863, column 2, paragraph 1, lines 15-19) and is protein chip as defined in the instant specification (USPGPUB paragraph 0063).

Regarding claims 1, 19 and 26, Liu et al do not teach about plastic substrate. However, a plastic substrate for immobilizing chain molecules were known in the art at the time of the claimed invention was made as taught by Obremski et al.

Obremski et al teaches an assay method comprising a plastic substrate (paragraph 0038) for immobilizing oligonucleotide probe (paragraph 0010). Obremski et al also teaches molecules immobilized on the plastic substrate stand up "vertically" from the surface (paragraph 0071). Obremski et al also teaches that plastic surface is optically transparent, has a higher refractive index than water, easy to configure to different dimensions and amenable for chemical coupling and is well suited for AFM and evanescent wave excitation method molecular detection (paragraphs 0038 and 0071).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the substrate of Liu et al with plastic substrate of Obremski et al with a reasonable expectation of success.

An artisan would have been motivated to modify the substrate of Liu et al with the expected benefit of having a plastic surface, that is optically transparent, having a higher refractive index than water, easy to configure to different dimensions and amenable for chemical coupling and is well suited for AFM and evanescent wave excitation molecular detection as taught by Obremski (paragraphs 0038 and 0071).

Regarding claims 1 and 19, Liu et al teaches the visualizing and identifying about 26 molecules in an 80.5 nm2 area (Fig. 3E, lane a2, area indicated by an arrow, pg. 865, column 1, paragraph 2). Obremski et al also teaches an AFM scanning of immobilized avidin array and further teaches that avidin extends 200 nm vertically from the surface and binds to biotin (paragraph 0071). Liu et al and Obremski et al do not teach about visualizing and identifying an individual chain molecule by scanning probe microscope in solution. However, visualizing and identifying an individual chain molecule by scanning probe microscope in solution was known in the art at the time of the claimed invention was made as taught by Seong et al.

Seong et al teaches visualization and identification of RecA protein binding to the single stranded DNA by scanning the complex by AFM in solution (Abstract, pg. 1288, column 1, and paragraph 1). Seong et al also teaches visualization and identification of single chain molecule (i.e., target DNA, Abstract). Combined teachings of Liu et al, Obremski et al and Seong et al, thus would provide a method of visualizing and

identifying a single strand DNA individual chain molecule uprightly immobilized on a plastic substrate by probing with an AFM scanning probe microscope in solution.

Seong et al also teaches that the AFM imaging allows to study small proteins binding to their individual target sequences under native conditions and for gene mapping on individual double stranded DNA for further enhancing the understanding of macromolecular interactions responsible for genetic and cellular regulation (pg. 1289, column 1, paragraphs 1 and 2).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the molecular detection method of Liu et al with the method of visualizing and identifying individual chain molecule of Seong et al with a reasonable expectation of success.

An artisan would have been motivated to modify the molecular detection method of Liu et al with the expected benefit of studying small proteins binding to their individual target sequences under native conditions and for gene mapping on individual double stranded DNA for further enhancing the understanding of macromolecular interactions responsible for genetic and cellular regulation as taught by Seong et al (pg. 1289, column 1, paragraphs 1 and 2).

17. Claims 1-3, 6-7, 19, 23-24 and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (USPN 7,033,476 filed Dec. 31, 2002) in view of Obremski et al (USPGPUB NO. 2002/0001853 published Jan. 3, 2002).

Regarding claims 1, 19 and 27-28, Lee et al teaches a molecular detection method comprising visualizing and identifying single molecules by probing with scanning probe microscope 78 in solution (Fig. 5, column 5, lines 40-52). Lee et al further teaches that a nanogate 42 is formed on the substrate 40 (Fig. 4,) and nucleic acid sample molecules are held at the gate by perpendicular electric field (Fig. 4, column 4, line 60, column 5, lines 53-58, column 8, lines 43-67), thus teaching single molecules are immobilized on a substrate and as immobilized being uprightly disposed relative to the substrate. Lee et al do not teach about plastic substrate.

Regarding claims 2 and 3, Lee et al teaches that single strand molecule is a protein (column 5, line 28).

Regarding claims 6, 7, 23 and 24, Lee et al teaches detecting and counting single molecule immobilized within the nanogate (column 8, lines 43-67) thus teaching number of detected molecules per unit area, thus giving the molecular localization information.

Lee et al do not teach about plastic substrate. However, a plastic substrate for immobilizing chain molecules were known in the art at the time of the claimed invention was made as taught by Obremski et al who teaches an assay method comprising a plastic substrate (paragraph 0038) for immobilizing oligonucleotide probe (paragraph 0010). Obremski et al also teaches molecules immobilized on the plastic substrate stand up "vertically" from the surface (paragraph 0071). Obremski et al also teaches that plastic surface is optically transparent, has a higher refractive index than water, easy to configure to different dimensions and amenable for chemical coupling and is

well suited for AFM and evanescent wave excitation method molecular detection (paragraphs 0038 and 0071).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the molecular detection method of Lee et al with the plastic surface of Obremski et al with a reasonable expectation of success.

An artisan would have been motivated to modify the molecular detection method of Lee et al with the expected benefit of having a plastic surface, that is optically transparent, has a higher refractive index than water, easy to configure to different dimensions and amenable for chemical coupling and is well suited for AFM and evanescent wave excitation molecular detection as taught by Obremski (paragraphs 0038 and 0071).

18. Claims 1, 19-27, 31 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al (USPGPUB 2003/0186311 filed Apr. 30, 2003, effective filing date May 29, 2009) in view of Liu et al (Nano Letters, 2002, 2, 863-867).

Regarding claims 1 and 19, Henderson et al teaches a molecular detection method comprising visualizing and identifying an individual chain molecule 10 (i.e., single molecule) immobilized on a substrate surface 12 and as immobilized being uprightly disposed relative to substrate surface 12 by probing with a scanning probe microscope (i.e., AFM) in solution (Fig. 1A and paragraphs 0040-0041, Example 4 and paragraphs 0089-0092). Henderson et al also teaches substrate comprise plastic substrate surface (paragraph 0029). Henderson et al also teaches observing a profile of

the substrate surface having individual antibody chain molecules 10 immobilized thereon (Figs. 1 and 2, paragraph 0047).

With regard to additional limitation of claim 19, Henderson et al teaches AFM molecular detection method comprising nucleic acid –nucleic acid interaction (paragraph 0023), thus clearly suggesting nucleic acid chain molecule immobilized on the substrate.

Regarding claims 21 and 22, Henderson et al teaches nucleic acid –nucleic acid, protein –nucleic acid interactions (paragraph 0023) thus suggesting complex comprises nucleic acid and protein molecules.

Regarding claim 23, Henderson et al teaches that the detecting a molecule comprises counting the number of detected chain molecules per unit area (Example 5 and paragraphs 0030 and 0098, Table 1).

Regarding claim 24, Henderson et al teaches that the counting the number of detected chain molecules per unit area, thus giving molecular localization information (Fig. 7, Example 5 and paragraphs 0030 and 0099).

Regarding claim 25, Henderson et al teaches a production process for a substrate with a chain molecule immobilized thereon, the production process as recited in claim 19 (Fig. 1 and paragraph 0041). Henderson et al also teaches AFM molecular detection method comprising nucleic acid –nucleic acid interaction (paragraph 0023), thus clearly suggesting nucleic acid chain molecule immobilized on the substrate.

Regarding claim 26, Henderson et al teaches that the substrate is a plastic substrate (paragraph 0029).

Regarding claim 27, Henderson et al teaches that the individual chain molecule 10, as immobilized, is uprightly disposed relative to the substrate surface 12 so as to extend substantially perpendicularly from substrate surface 12 (Fig. 1 and paragraph 0041) and further teaches substrate comprises plastic surface (paragraph 0029).

Regarding claim 31, Henderson et al do not teach DNA chip.

Regarding claim 33, Henderson et al teaches that the profile is observed using atomic force acting between the substrate surface having the individual chain molecules immobilized thereon and a probe of the scanning probe microscope (Fig. 1 and paragraphs 0058-0062). Henderson et al also teaches AFM is used to profile binding force as a result of molecular interaction between probe on the substrate surface and the binding partners and rupture force to break the said molecular interactions (paragraphs 0052-0053), which is reasonably interpreted as atomic force in view of lack of limiting definition for "atomic force" in the instant specification.

Regarding claim 34, Henderson et al teaches that the profile is observed by measuring an amount of rupture force, i.e., flexing of probe caused by disruption of molecular interaction between the binding partner and probe on the substrate force (paragraphs 0051-0054). The "rupture force" of Henderson et al is reasonably interpreted as atomic force in view of lack of limiting definition for "atomic force" in the instant specification.

As described above, Henderson et al teaches AFM molecular detection method comprising nucleic acid –nucleic acid interaction (paragraph 0023), thus clearly suggesting nucleic acid chain molecule immobilized on the substrate. However, nucleic

acid immobilization on the substrate surface was known in the art at the time of the claimed invention was made as taught by Liu et al.

Liu et al teaches a molecular detection method comprising visualizing and identifying chain molecule (Figs. 4A and 4G, pg. 865, column 2, paragraph 3) immobilized on a substrate and as immobilized being uprightly disposed relative to said substrate so as to observe a profile of the substrate surface having chain molecule immobilized there on (Figs. 1 and 4C, pg. 865, column 1, paragraph 1) by probing with scanning probe microscope in solution (Abstract, Figs. 3A and 4A, pg. 865, column 2, paragraph 2), wherein the molecule immobilized on the substrate is a nucleic acid (Fig. 2, pg. 864, column 1, paragraph 3).

Teachings of Liu regarding limitations of claims 21, 22 and 25-34 are described above in section 16.

Liu et al also teaches that immobilization of nucleic acid chain molecules on the substrate surface allows better understanding of orientation of DNA molecule with respect to substrate surface which would benefit fabrication of DNA biosensors and biochips (pg. 866, column 2, paragraph 2)

Both Henderson et al and Liu et al teach molecular detection method by probing with scanning probe microscope in solution and both teach nucleic acid protein interactions (Henderson Figs. 7 and 8; Liu Fig. 4). Therefore method steps are combinable. Having method steps for immobilizing nucleic acid molecule on the substrate surface is beneficial in the molecular detection method of Henderson for

determining the orientation of the immobilized nucleic acid chain molecule for fabricating better DNA biosensors and biochips.

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the immobilized molecules on the surface in the molecular detection method of Henderson et al with the nucleic acid chain molecules of Liu et al with a reasonable expectation of success.

An artisan would have been motivated to modify the immobilized molecules on the surface in the molecular detection method of Henderson et al with the expected benefit of better understanding the orientation of DNA molecule with respect to substrate surface which would benefit fabrication of DNA biosensors and biochips as taught by Liu et al (pg. 866, column 2, paragraph 2).

Response to remarks from the Applicants

Claim rejections under 35 U.S.C. § 103(a)

19. Applicant's arguments filed on August 27, 2009 over combination of references have been fully considered (Remarks, pgs. 9-22). These arguments are not persuasive for the following reasons.

Applicant's main arguments are directed towards cited art neither disclosing nor suggesting a molecular detection method as in the present claims especially observing the profile using atomic force acting between the plastic substrate surface having the individual chain molecules immobilized there on and a probe of the scanning probe microscope. Applicants further asserts neither of the cited references teach nor suggest

observing the profile by measuring flexing of the probe caused by atomic force (Remarks, pg. 10, paragraph 3). These arguments are not persuasive because neither instant claims nor specification provide limiting definition or steps or nature of the "atomic force" or "flexing probe". Therefore claims have been given the broadest reasonable interpretation. Given the broadest reasonable interpretation, teachings of Liu et al of frictional force generated by methyl groups on the substrate surface and probe of the scanning probe encompasses the "atomic force" (section 16). Also, teachings of Liu et al measuring the change in the profile of chain nucleic acid molecule interacting with DNase I encompasses amount of flexing of probes caused by the interaction force between nucleic acid and DNase I (i.e., atomic force). Furthermore, as described above in section 13, Henderson et al also teaches "atomic force" and "flexing probe". For these reasons argument s are not persuasive.

Applicants reiterate the previous arguments regarding the teachings of Liu et al, Seong et al and Obremski et al especially DNA protein complex and immobilizing chain molecules on the plastic substrate (Remarks, pgs. 13-18). The arguments have been addressed adequately in the previous office actions and responses on the record are still valid. Furthermore, Applicants argument directed to attacking individual reference of Liu et al, Obremski et al and Seong et al are not persuasive because claims have been rejected with combination of cited references. As described above in section 16, Liu et al teaches all the steps as recited in claims 1 and 19, except for plastic substrate and visualizing and identifying an individual chain molecule. Obremski teaches plastic substrate and provides teachings, suggestions and motivation for using

a plastic substrate. Seong teaches visualizing and identifying an individual chain molecule and provides teachings, suggestions and motivation. For these reasons arguments are not persuasive.

Applicants further argue that one of ordinary skill in the art need not visualize nanopatterns of the single stranded DNA molecules because one could not observe the entire structure. Applicants further assert that Liu would not suggest "molecular detection methods" (Remarks, pg. 15, paragraph 2). These arguments are not persuasive because Liu et al teaches "structure of the nanopattern and the relative orientation of the single stranded DNA in situ using AFM and further teaches that the DNA molecules have stand up orientation" (pg. 866, column 2, lines 3-6). Furthermore, Applicants have provided any factual evidence to support the asserted "not observing the nanopatterns of the DNA molecules by AFM". For above reasons arguments are not persuasive.

Applicant further argue that Seong et al teaches visualizing and identifying DNA protein complexes adsorbed in parallel to the mica surface and therefore would have neither disclosed nor would have suggested such visualizing and identifying an individual chain molecule uprightly disposed relative to the substrate (Remarks, pg. 18, paragraph 2). This argument is not persuasive because Seong et al teaches a step of visualizing and identifying an individual DNA chain molecule (abstract). Liu et al teaches DNA molecule uprightly disposed on the substrate (pg. 866, column 2, lines 3-6).

Applicants further argue that Lee et al neither disclose nor suggest the claimed molecular detection method and teach away from the claimed method (Remarks, pgs.

18-21). This argument is not persuasive because as described above in section 17, Lee et al teaches single nucleic acid molecules are held at the nanogate by perpendicular electric field, i.e., molecules are uprightly disposed relative to the substrate as claimed and molecules are visualized, identified and counted at the gate by scanning probe microscope in solution.

Applicants further argue that in Lee et al molecules are counted one by one as each of them passes through the detection gate and single molecules have to move through the gate and therefore would not have looked for the plastic substrate of Boesky (Remarks, pg. Pg. 19, paragraph 2, pg. 20, paragraph 1). These arguments are not persuasive because claim merely requires visualizing and identifying individual chain molecules immobilized on a substrate and teaching of Lee of detecting individual molecule uprightly disposed at the nanogate intersection comprising substrate surface meet the limitation of immobilized on the surface. Furthermore, Obremski teaches plastic substrate and provides teachings, suggestions and motivation for using a plastic substrate. For these reasons arguments are not persuasive.

Conclusion

20. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Narayan K. Bhat

Examiner, Art Unit 1634

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634